APPROACHES TO NON-CONTACT ANTERIOR CRUCIATE LIGAMENT INJURY STUDIES: UTILITY OF OPERATIONS RESEARCH AND ARTIFICIAL INTELLIGENCE

Nicholas Ali[1], Gholamreza Rouhi[2,3], Gordon Robertson[1]
[1] *Department of Health Science, School of Human Kinetics, University of Ottawa, Ottawa, Canada*
[2] *Department of Mechanical Engineering, University of Ottawa, Ottawa, Canada*
[3] *Faculty of Biomedical Engineering, AmirkabirUniversity of Technology, Tehran, Iran*
E-mail: nali065@uottawa.ca

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Abstract

A multidisciplinary design optimization (MDO) approach is proposed to aid in the prediction of non-contact anterior cruciate ligament (ACL) injury mechanisms and risk factors. In this investigation the need for such an approach is argued based on an exhaustive evaluation of diverse factors that cause non-contact ACL injury, and the similarly numerous and different existing study approaches that have been carried out to investigate injury. The proposed MDO approach fuses patient data and existing study approaches via an artificial intelligent (AI) technique—absent in previous biomechanics investigations—so as to offer new insights into ACL injury prevention.

Keywords: ACL injury; multidisciplinary design optimization; operations research; artificial intelligence.

ÉTUDES DES APPROCHES SUR LES RUPTURES DU LIGAMENT CROISÉ ANTÉRIEUR SANS CONTACT : UTILITÉ DES RECHERCHES OPÉRATIONNELLES ET INTELLIGENCE ARTIFICIELLE

Résumé

Une approche de conception optimale multidisciplinaire (MDO) est proposée comme outil de prévision du mécanisme de rupture du ligament croisé antérieur LCA et les facteurs de risque. Dans cette étude, le besoin d'une telle approche est discuté sur la base d'une évaluation exhaustive des différents facteurs qui causent les ruptures du ligament croisé antérieur sans contact LCA, et plusieurs études similaires avec des approches courantes qui ont été réalisées pour investiguer les causes des ruptures. L'approche MDO proposée fusionne les données du patient et les approches existantes via une technique d'intelligence artificielle pour ainsi avoir de nouvelles données sur la prévention des ruptures du LCA.

Mots-clés : rupture de LCA; optimisation de la conception multidisciplinaire; recherche opérationnelle; intelligence artificielle.

1. INTRODUCTION

The anterior cruciate ligament (ACL) is an intra-articular ligament of the human knee joint that connects the tibia and the femur. The ACL comprises of two bundles named after the location of their respective tibial attachment sites: anteromedial (AM) and posterolateral (PL) [1]. The average ACL length is approximately 32 mm and the average width is approximately 11 mm [2]. The primary function of the ACL is to restrain anterior tibial translation (ATT) [3]. The ACL also acts as a secondary restraint to internal tibial rotation in the non-weight-bearing knee [3,4]. Some studies have estimated that the ACL has a load to failure of approximately 2160 N, stiffness of 242 N/mm^2 and a failure strain of up to 20% for young adults [5,6].

ACL injuries that occur without physical contact with another person or object are referred to as non-contact ACL injuries [7]. Approximately 70% of ACL injuries occur as a result of non-contact events which amounts to an annual cost of almost one billion dollars in the United States alone [8,9]. This does not account for the 31% of patients who require revision surgery approximately five years after ACL reconstruction [10,11]. Even though the precise mechanisms of non-contact ACL injury are unknown, research has implicated a number of non-contact ACL injury mechanisms (see Fig. 1) and risk factors [12,13]. The identification of the mechanisms and risk factors for non-contact ACL injury is prevalent in the literature and this is partly motivated by the need to develop prevention programs and training regimes that can potentially reduce the risks of sustaining injuries. From Fig. 1, it can be gleaned that non-contact ACL injury likely occurs from combined loading to the knee joint [14–17]. This suggests that non-contact ACL injury possibly occurs when many risk factors and extreme conditions happen simultaneously. Non-contact ACL injury is also a whole body phenomenon that is best analyzed by simultaneously addressing multiple risk factors of which neuromuscular control, joint kinematics and geometry, as well as, external forces that may be the most important. The five existing study approaches employed to obtain a better understanding of the mechanisms and risk factors of non-contact ACL injury are: clinical studies, interviews with athletes, video analyses, computational modeling and experiment. Of these study methods, clinical studies,

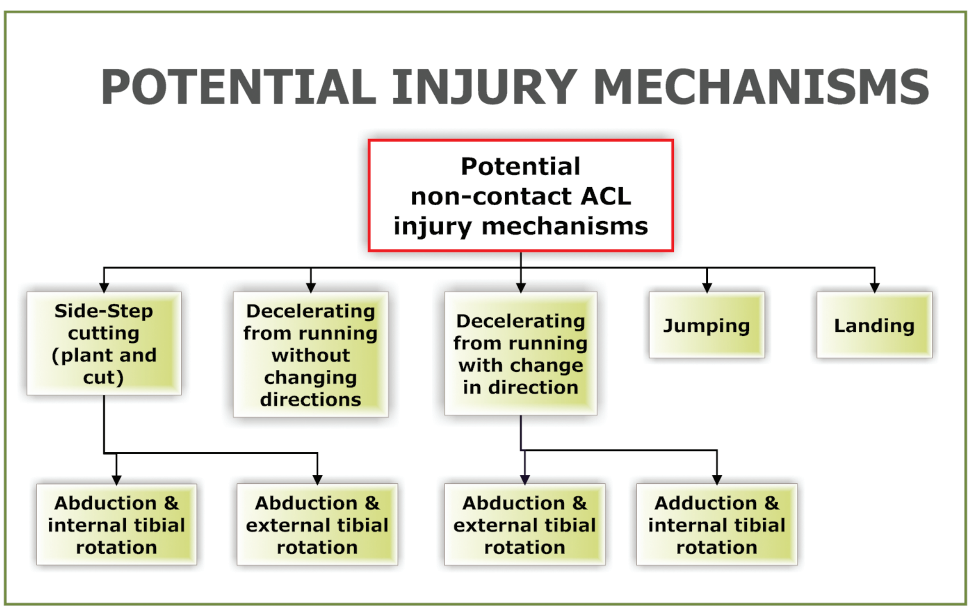

Fig. 1. Possible mechanisms of non-contact ACL injury.

interviews with athletes and video analyses are qualitative approaches providing mostly descriptive data and as a result are not adequate for obtaining a comprehensive understanding of injury mechanisms to the ACL. The current literature indicates the two main quantitative approaches used to investigate ACL mechanics, namely, computational modeling and experiments. Further details on these study approaches along with their strengths and weakness are presented by Krossburg et al. [18] and Ali et al. [19]. These study approaches cannot simultaneously capture the many contributing factors, unknowns, variabilities, uncertainties, constraints, and loading situations responsible for ACL injury. As well, these study approaches have provided valuable information but do not offer a comprehensive view of ACL injury mechanism. Therefore a necessary first step to a possible approach aimed at simultaneously capturing many of these parameters entailed in non-contact ACL injury research is deciding on a solution strategy. The authors' view is that many of the challenges confronting studies aimed at reinforcing our understanding of non-contact ACL injuries may be better addressed using optimization.

Operations Research (OR) is a domain of optimization that applies advanced analytical methods to better facilitate decision making. Operations research takes an interdisciplinary approach to manage and solve problems in business, industry, government, etc. Many OR methods are thought of as traditional methods of optimization partly due to the need to have a tailored problem definition, the high computational time incurred, and the inability to handle a large search domain. Many OR techniques such as gradient based methods cannot be applied to the problem of how and why non-contact ACL injuries occur because of the absence of a polynomial-type function, the need to obtain derivatives, and the difficulties with handling numerous design parameters and design constraints in a large search domain. Hence, from an OR perspective, there are specific problems and specific procedures for solving these problems (see Table 1). It is the wording or problem definition that helps us decide which OR method to employ. Therefore, a given procedure requires certain types of attributes in the problem statement to enable us to decide which OR strategy to use to solve the problem. This has somewhat limited the range of application and robustness of OR procedures for solving complex problems.

Artificial intelligence (AI) provides another domain of optimization. Artificial intelligence is the science and engineering of making intelligent machines, especially intelligent computer programs. Hence, computer systems can be imbued with behaviors that would be regarded as

Table 1. OR problems and corresponding solution method.

Examples of OR problems	Corresponding Procedure [20]
Minimize some quantity subject to certain constraints being satisfied	Mathematical programming algorithms
Determine the quantity of an item (having certain demand, holding cost, and order cost)	Economic order quantity formulas
What is the earliest or latest starting time for some activity?	Network analysis algorithms
What is the expected return for a particular investment?	Expected value calculations
Determine a forecasting function based on historic data	Regression algorithms
Forecast a quantity	Forecasting functions
How many servers should be in place?	Queuing theory methods
What are the impacts of altering a system in particular ways?	Simulation algorithms

intelligent if witnessed in a human [20]. In addition, AI focuses on discovering new ideas and techniques which exhibit increased degrees of intelligence. The interest in optimization via AI techniques is linked to [21–25]: 1) The need to solve complex problems; 2) The system-based type of solution offered; 3) The need to handle a large multimodal search space; 4) The frequent requirements to incorporate qualitative and quantitative design variables; 5) The improved capability to locate the global optimum; and finally, 6) The improvement in the efficiency of readily available traditional methods of optimization.

Rather than presenting a historical review of the application of optimization to the biomechanics field, this paper takes a more direct approach discussing the work in four fields: 1) Commonly used OR and AI techniques; 2) Present challenges with existing study approaches used for non-contact ACL injury research; 3) State of the art in utilizing OR and AI techniques in non-contact ACL injury research; and finally, 4) How optimization and existing non-contact ACL injury study approaches can be united to address some of the present challenges in ACL injury research.

1.1 Operations Research (OR) Optimization Techniques

The minimization or maximization of a function $f(x)$ without any constraints on x is called unconstrained optimization. Introduction of constraints into an optimization problem is called constrained optimization. This type of problem formulation is called mathematical programming. Mathematical programming can be subdivided into linear and non-linear programming. The major characteristics of linear programming (LP) are that the objective function and also its associated constraints should be linear. In addition, constraints must be expressed in terms of decision variables [26,27]. An integer programming problem (IPP) is a LP problem in which the design variables are restricted to be non-negative integers only; otherwise, it is called non-integer programming problem. A problem that entails a quadratic objective function subjected to linear constraints is called a quadratic programming problem (QPP) [28]. To date, the range of application of mathematical programming methods is limited partly because real world problems cannot be accurately modeled by linear relationships, the input data are seldom known with accuracy, as well as the exhaustive nature of the search approach. Because of the high number of OR techniques and considering the scope of this paper, it is not feasible to discuss these techniques in depth here. Nonetheless, to garner an in depth knowledge of OR techniques as well as their capabilities and applicability, readers are encouraged to consult [26,29,30]. Also, specific details aboutunconstrained optimization methods in OR can be obtained by consulting the following references [31–36]. For further details and implementation of some commonly used constrained optimization methods of OR, the following references may also be consulted: the simplex method [29], goal programming [37], Newton-Raphson method [31], integer programming [29,38], and the Monte-Carlo method [39–42].

1.2 Artificial Intelligence (AI) Optimization Techniques

For many practical problems encountered, the only way to be sure of finding an optimal solution is to search completely through the whole set of possible solutions. If there is a very large, but finite number of possible solutions, the idea of an exhaustive search is tempting and often quite easy to implement into a computer program. The drawback however is that this requires lengthy computational time. The time required to carry out such an exhaustive search is - although finite - far greater than is tolerable. The challenge then is to find short-cuts that will allow one to organize the search process so that it is no longer a complete search over all possible solutions, but rather it becomes an affordable search that is likely to find optimal or

near optimal solutions [43]. These methods are called AI or heuristic methods. AI techniques are often applied to computationally intractable non-deterministic polynomials (NP), simply because the best (most efficient) methods we know of for solving these problems exactly (or optimally) can take an exponential amount of computational time [44]. For small search spaces, classical exhaustive OR methods such as mathematical programming usually suffice; however, for larger search spaces special AI techniques must be employed. Some commonly used AI methods that are constantly being improved and utilized are: tabu search, simulated annealing, genetic algorithms, and artificial neural networks. Given the focus of this paper, coupled with the fact that the concepts in AI are rather complex and the field is so vast, it is not possible to explore all details of AI techniques here. Nonetheless, attempts are made to impart a flavour of these techniques in this article, and the insight they can bring to non-contact ACL injury studies. For in-depth readings on AI techniques and its applications, readers are encouraged to consult [45,46]. Specific details on some commonly used AI techniques and their capabilities can be obtained by consulting the following references: tabu search [44,47,48], simulated annealing [26, 49–52], genetic algorithms [53–61], and artificial neural networks [46, 62–64].

2. PRESENT CHALLENGES WITH EXISTING APPROACHES USED FOR NON-CONTACT ACL INJURY RESEARCH

There has been much interest in quantifying the ACL loading in-vivo during activity [73]. This is motivated by the high incidence of ACL injury, lack of clear understanding of ACL mechanics, and frequent need for surgical treatment. Nonetheless, there are many challenges with existing study approaches aimed at improving our understanding of non-contact ACL injury and a brief description of some of these are highlighted below.

First and foremost, many studies have pointed out that several intrinsic and extrinsic risk factors are responsible for non-contact ACL injuries [65–67]. However, some studies address only one risk factor and investigate its effects on ACL rupture [68–70]. It seems quite unlikely that only one risk factor will be responsible for ACL injuries. A reasonable surmise is that a non-contact ACL injury could be multifaceted occurring from a complex interaction of multiple risk factors and taking place when many extreme conditions happen simultaneously. Recognizing that the type of study approach used is dependent on the question posed, perhaps many research groups are compelled to focus on only one or a few risk factors or adapt a reductionist approach to solving problems in ACL mechanics given the limitations with existing study approaches. Secondly, many non-contact ACL injury studies are experimental and as such have the inherent limitation of cost, noise, low sensitivity, and difficulty of measuring stresses or strains [71,72]. To elaborate, experimental studies to understand non-contact ACL injuries can be categorized as in-vivo and in-vitro. In-vivo testing is conducted with living subjects and involves the connection of a strain transducer to the ACL. Given the location and size of the ACL, in-vivo studies using strain transducers are limited to measuring strain in the AM bundle of the ACL for movement in the sagittal plane only [73]. Moreover, these studies are limited to knee flexion angles greater than 15 degrees due to potential impingement of the strain transducer with the femoral notch [16] which limits this approach ability to predict injury. Ethical standards controlling human and animal testing limits the use of in-vivo testing given it is invasive. In addition, the vast majority of empirical studies investigating non-contact ACL injuries are in-vitro. In-vitro testing is non invasive and typically entails the use of human cadavers. Some major challenges with in-vitro studies using cadavers is the inability to include muscle activation and muscle forces, as well as, inability to obtain repeatable results. Other

existing study approaches such as clinical studies, interviews with athletes and video analysis are all qualitative and as such cannot provide a comprehensive understanding of non-contact ACL injury mechanisms. Finally, computational modeling approaches used to study non-contact ACL injury, specifically, mathematical [74,75], musculoskeletal [76,77], and finite element modeling [78–80] when employed on their own offers a limited understanding of non-contact ACL injury mechanics. For example, musculoskeletal model provides great details on joint kinetics, muscle activation and muscle forces but cannot determine the load to failure of a ligament [81,82].

An overarching challenge with all existing non-contact ACL injury study approaches is their inability to handle high variability. There is much variability in hard and soft tissue geometries due to subject's age, race and gender, as well as, large variability in tissue material properties due to subject's age and gender when compared to engineering structures which have mostly unvarying geometries and material properties. In addition, there are many inter- and intra-subject variabilities such as muscle activation patterns during experiments over which the researcher has little control. Inter-subject variabilities may be associated with type of shoes used, surface on which task is performed, normalization method, and electrode placement [83,84]. Intra subject variabilities may stem from technician performing experiments and can be high [85]. Moreover, non-contact ACL injuries occur from a variable number of movement patterns. Given these variabilities, in many cases it is difficult to compare the results from one study to another due to the tremendous heterogeneity between studies. It can be argued that these variabilities partly exist because of the lack of standards and perhaps specifications for testing in the field of biomechanics.

3. STATE OF THE ART IN UTILIZING OR AND AITECHNIQUES IN NON-CONTACT ACL INJURY RESEARCH

There has been little research on utilizing OR or AI techniques to facilitate a better understanding of non-contact ACL injuries. Studies utilizing OR techniques to deal with non-contact ACL injury is highlighted below followed immediately by those utilizing AI techniques.

Using a 3D mathematical model, Blankevoort et al. [86] studied the articular contact surface of the knee to compare a rigid and deformable contact scenario. The surface of the femur and tibia as well as the ligaments and articular cartilage were modeled. The model was developed using the work of Wisman et al. [75] but incorporated deformable articular contact description similar to Essinger et al. [87] and An et al. [88]. A later study by Blankvoort et al. [89] used the same mathematical model to estimate the initial strains of the ligaments of the knee joint for usage in the model since no experimental data was available. Blankvoort research group employed an optimization scheme to estimate the initial strains since no experimental data was available. Their optimization method was based on minimization of the difference in terms of kinematic parameters between the developed knee model and experiments via the variation of the reference strains in the ligament. The minimization scheme was based on a modified Levenberg-Marquardt algorithm (LMA) [90]. The LMA is an iterative technique used to locate the minimum in a multivariate function hat is expressed as the sum of squares of non-linear real valued functions [91]. Levenberg-Marquardt algorithm can be thought of as a combination of steepest decent and the Gauss-Newton method. This method is especially useful for problems where the initial guess is unknown and may be far from the final minimum. This method was modified by Flectcher [92] to tailor the amount of dampening use at each iteration so as to improve the robustness of the algorithm through rate convergence, entrapment in local minimum, and system stability. This optimization scheme was also later utilized to estimate the reference lengths of the ligaments and stiffness of the meniscus in a finite element model study of

the human knee joint by Li et al. [80]. The same study approach and optimization routine was also later used by this same research group to undertake parametric studies of knee kinematics, ligament forces, and contact pressure in response to simulated muscle loads [93]. An analytical modeling study by Pandy et al. [94] found that hamstring co-contraction decreases the anterior shear force applied to the tibia, thereby reducing the ACL forces at small flexion angles. The authors used a non-linear programming algorithm developed by Powell [95] to solve aan over constrained system of equations via least squares optimization. Pandy's research group furtheredthe development of this model [81,96] by applying thisidentical optimization approach and subsequently concluded that the knee is one part of a kinetic chain and that the trunk, hip, and ankle may contribute to ACL injury. Shelburne et al. [97], from the same research group as Pandy et al., also employed the same optimization approach to calculate the forces developed in the muscles and forces transmitted to the knee ligaments during squatting. Shelburne et al. [98] also developed a dynamic feature to this optimization approach to calculate muscle forces during gait. The optimization routine centered on finding the muscle excitation histories, muscle forces, and body motions subjected to an objective function geared towards minimizing metabolic energy consumed per unit distance moved. Greater details on this dynamic optimization approach used by Shelburne et al. [98] are reported in [99]. Pflum et al. [100] also from the same research group as Pandy et al., also employed this dynamic optimization method to investigate the forces transmitted to the ACL during a soft style drop landing.

McLean et al. [76,101] used a forward dynamics musculoskeletal model of the lower extremity to study side step cutting dynamics that may cause injury to the ACL. The authors used an AI technique, specifically, simulated annealing to determine the muscle activation patterns that best replicated a subject's kinematics and kinetics [76,101]. A Monte Carlo simulations were also performed by the authors to determine the effects of variability in neuromuscular control on peak anterior drawer force, valgus moment, and internal rotation moment [101]. Monte Carlo methods are algorithms that randomly generate and retain the best solutions before going to the next search iteration. Monte Carlo method is used primarily in this application to evaluate the probability of random outcomes of human movement. MonteCarlo simulation is an attractive tool since it allows researchers to study and predict risk ofsustaining an injury before injury occurs. To the best of our knowledge, this is the only research group that has utilized an AI technique to better understand ACL injury mechanisms. However, simulated annealing is simply mentioned by the authors but the way the method is employed to answer the author's research question is not clear. Mclean et al. [14] also applied the identical optimization methods to examine whether sagittal plane knee loading during side step cutting could in isolation injure the ACL. As well, a recent study by the same group of researchers utilized the same approach to determine the potential for perturbations in key initial contact neuromuscular parameters to injury of the ACL [101]. Lin et al. [102] modified the model developed by McLean et al. [101] to estimate the ACL injury rate for a stop jump task. The study was geared towards validating a stochastic biomechanical model so as to examine the role of gender as a risk factor for non-contact ACL injury.

4. FUSING OPTIMIZATION WITH EXISTING NON-CONTACT ACL INJURY STUDY APPROACHES

Many real-world problems today involve the interaction of many disciplines which is particularly the case in many biomechanics research projects. As a result, tying together concurrent activities involving many disciplines with an optimization technique has become

popular [103–105]. More specifically, MDO has emerged as a field of research and practice that brings together many previously disjointed disciplines and tools of engineering. Multidisciplinary design optimization can be described as a technology and a methodology for the design of complex, coupled engineering systems, such as an aircraft [106]. Typically MDO involves many design variables, many constraints, and analysis from various contributing disciplines, where coupling between disciplines and conflicting requirements exist.

From a review of the literature, it does appear that research in non-contact ACL injury studies is fragmented, presented with many challenges, and limited in utilizing optimization. Many study approaches provide valuable information but do not offer a comprehensive view of ACL injury mechanism. To address some of these challenges, we believe that a MDO methodology should be employed. The authors' approach entails combining the five existing study approaches of non-contact ACL injury studies using an AI technique in a MDO paradigm (see Fig. 2). Such a study approach may be a much more robust and comprehensive methodology to better predict non-contact ACL injuries [107,108]. An AI technique is preferred over OR techniques for non-contact ACL injury studies since they do not require a mathematical function, are more robust in dealing with both qualitative and quantitative variables, enables a system-based type of approach to solving complex problems [109], and above all, they share an enhanced ability to handle many design variables and constraints over a large multimodal search space [20,110]. The AI technique is employed to orchestrate the fusion of the two quantitative study approaches in the MDO paradigm, as well as, to facilitate search and parameter identification. In this approach, the three qualitative study approaches are used for results validation. An AI technique also enables one to capture the wide variability in movement patterns to cause injury, and in tissue material properties, numerous design variables, numerous design constraints, many risk factors, and multiple objective functions.

From Fig. 2, it can be noted that many disciplines, much hardware and software, many experts, and a high level of effort are required to develop this proposed approach. As can be observed, starting with the patient bio-data in the form of MRI and/or CT scans of the joint or tissue of interest, a finite element model (FEM) was constructed. This FEM should include the major bones, joints, muscles, tendons, and ligaments of the lower extremity. Testing in a gait lab is conducted using human subjects instrumented to collect joint kinematics, muscle activation, and ground reaction forces for close to injury type motion. Some of these metrics are then supplied to a musculoskeletal rigid body modeling software such as AnyBody. The musculoskeletal models can then be validated with electromyography (EMG) data collected as well as published data. The outputs from the musculoskeletal model are the muscle activation, muscle forces and joint kinetics. The body kinematics and external forces from experiments, as well as muscle forces and muscle kinematics from musculoskeletal modeling will form the boundary conditions for the FEM.

The AI technique can be used to vary the inputs to the FEM until the output kinetics are within an order of magnitude of kinetics determine from inverse dynamics analysis of the musculoskeletal model. The calculated error from this exercise once within a reasonable threshold can be used as a metric to determine if the model can be considered validated. Major bones of the FEM such as the femur can also be modified, constrained, and loaded in an identical manner to replicate published results from three and four point bending experiments to further aid FEM validation. The validated FEM can then be used to study a specific non-contact ACL injury mechanism with the aid of the AI technique. To accomplish this a problem is defined and formulated to determine the instance where many risk factors, many forces, and other extreme conditions happen simultaneously to cause ACL failure. The objective function

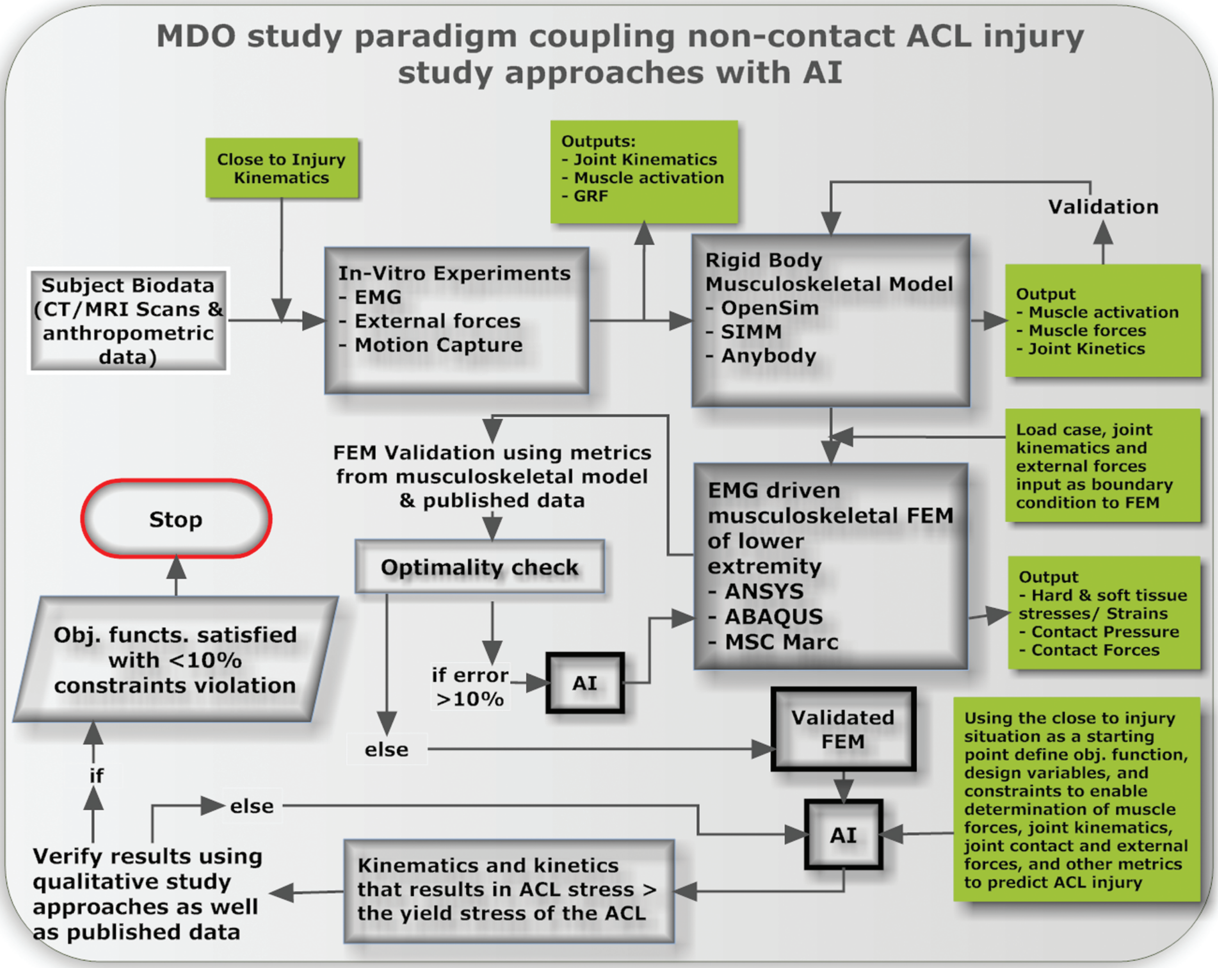

Fig. 2. A possible multidisciplinary and coupled study approach to address present challenges in non-contact ACL injury research.

can be geared towards finding the precise lower extremity kinematics that result in ACL stresses beyond its yield stress. The external forces, muscle activation, and muscle forces at this specific lower extremity kinematic should be compared to published data for the specific injury mechanism studied. As well, to ensure practicality, results in the literature from the three qualitative study approaches can be consulted and compared to results obtained from this simulation.

This MDO methodology should first be used to investigate very simple human movements for developmental and validation purposes, and then later be employed to study more complex motions such as side step cutting manoeuvres.

For each stage of this MDO paradigm verification and validation is mandatory. For example, if a genetic algorithm is used as the optimization technique then this technique must be verified and validated against benchmark mathematical functions, as well; if musculoskeletal models are employed they too must be validated against measured EMG data as well as published data. This MDO methodology should allow for automatic or semiautomatic data exchange between experimental, musculoskeletal modeling, and FEM study approaches under a

single software GUI. For example, data exchange algorithms and an AI technique programmed in Matlab can be used to fuse a FEM software such as ANSYS and a musculoskeletal modeling software such as AnyBody via batch processing. Essentially, ANSYS or AnyBody can be called up in batch mode to retrieve or send data using Matlab. This fusion should allow for dynamic data exchange between software packages. The outputs from the musculoskeletal model and finite element model can be validated with published and experimental data. This type of multidisciplinary and integrated biomechanics study paradigm is seem to be absent from the current literature.

5. SUMMARY AND CONCLUSIONS

A brief overview of the two main domains of optimization, namely, OR and AI, along with commonly used techniques within these two domains were presented. Some of the limitations of existing non-contact ACL injury study approaches confounding our understanding of ACL mechanics were then presented. A review of the literature aimed at identifying non-contact ACL injury studies utilizing OR or AI techniques was conducted. Finally, a new approach aimed at uniting optimization with the five existing non-contact ACL injury study approaches in a MDO study paradigm was proposed.

It was shown that present challenges in non-contact ACL injury studies stem partly from the inability of existing study approaches to simultaneously capture numerous factors and parameters which are at play during ACL injury. These factors and parameters include, but not limited to, biomechanical, environmental, anatomical and hormonal variables [111,112]. Many studies have concluded that these factors are responsible for non-contact ACL injuries but a large number of them have focused only on one aspect of the ACL injury mechanism, thereby failing to capture all factors at once as well as simultaneously considering the interactions of the different parameters involved. It was also determined that there are few attempts to use either OR or AI techniques in the non-contact ACL injury research, with OR techniques being more prevalent. It was also established that an AI technique is better suited to address present challenges in non-contact ACL injury research because of its robustness.

To address the limitations of existing non-contact ACL injury study approaches the possibility of a coupled MDO study paradigm was proposed. This proposed approach intends to enable seamless data exchange from many existing study approaches. Another possible advantage of this approach is its possible ability to handle wide variabilities and simultaneously take into account many factors, constraints, unknowns, and uncertainties. Hence, this approach could potentially provide a tool that enables one to have a better global view of the effects of changing numerous contributing factors on non-contact ACL injury. However, this methodology is quite complex and costly and requires tools, expertise, and information from various fields of bioengineering.

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